REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

New claim 19 is added. New claim 19 is supported by the present specification, at least with respect to paragraphs [0039] and [0046]. No new matter is added to the application. Claims 1-19 are pending in the application. Re-examination and reconsideration of the application, as amended, are requested in view of the following remarks.

The present Amendment is responsive to the new Office Action dated November 14, 2007. That Office Action was issued, after Applicant's prepared and filed a Notice of Appeal and an Appeal Brief, responding to the Final Office Action of January 16, 2007. The new Office Action dated November 14, 2007, withdraws the rejections based on prior art that were raised in the January 16, 2007, Office Action, but re-opens prosecution to raise new grounds of rejection that were not previously raised. The new grounds of rejection relate to claim language that has been present in the application claims for years (and, in some cases, from the original 2003 filing of the application), yet the new rejections were not previously raised in any of the Office Actions received prior to the November 14, 2007, Office Action. Rather, the new grounds have been raised, after the Applicant has successfully overcome previously raised rejections.

In addition, new grounds of rejections have been presented that are based, in part, on the same Valdes et al. reference that Applicant discussed in its Appeal Brief (to successfully overcome previous rejections that were based, in part, on the Valdes et al. reference). Applicant's Appeal Brief addressed and overcame a rejection based on an attempt to combine Valdes et al. with another reference (article authored by Hatzinikolaou et al. and U.S. Patent No. 6,117,679 to Stemmer). In particular, Applicant overcame that rejection by pointing out that Valdes et al. teaches away from the combination by, instead, teaching to address the peroxide degradation problem by using additives to neutralize the peroxide.

Thus, Applicant has already shown that Valdes et al. teaches away from combining other references that describe general mutation processes. However, the new grounds of rejections are based on the Examiner's suggestion to combine Valdes et al. with the Cherry et al. article and

Hatzinikolaou et al. references in the same manner in which the Examiner previously attempted to combine the Valdes et al. reference with the document titled Stemmer and Hatzinikolaou et al. Because the Valdes et al. reference itself (and other prior art of record), teaches away from the claimed invention, the new grounds of rejections based, in part on Valdes et al. are improper for the same reason as set forth in Applicant's Appeal Brief with regard to combining Valdes et al. with the Hatzinikolaou et al. and Stemmer references.

In the present Amendment, Applicant has addressed each of the grounds of rejection raised in the new Office Action dated March 8, 2006. In view of the present response, the lengthy prosecution history, the withdrawal of most of the previous rejections, and the recent introduction of a number of new rejections relating to claim language that was present in the claims for years or that are similar to the prior-art rejections that Applicant already overcame in the Appeal Brief, Applicant requests an allowance of the present Application.

1. Response To Rejection Under 35 U.S.C. 112, Second Paragraph:

Claims 7-10 and claims 11-18 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed. Applicant requests that the rejection be reversed and the rejected claims allowed in view of the following remarks.

In explaining the rejection the Examiner stated:

Claims 7-10 recite the phrase "predefined, desired functionality". The metes and bounds of this phrase in the context of the above claims are not clear to the Examiner. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear to the Examiner either from the specification or from the claims as to what specific "functions" of glucose oxidases are encompassed in the phrase "predefined, desired functionalities".

This rejection is respectfully traversed. In particular, it is submitted that the original specification provides an example of the term "predefined desired functionalities" in various location, such as, paragraphs 2 and 23. Similarly, one skilled in the art would understand how to define a desired function of the enzyme. A person of ordinary skilled in the art could not be formulating enzymes without some predefined (preconceived) goal (desired function). Accordingly, one with ordinary skill in the art would screen for predefined, desired functions when formulating the enzyme.

For example, paragraph 2 of the original specification states:

"formulating a glucose oxidase enzyme possessing a certain desired property or properties, and, in particular embodiments, for formulating a glucose oxidase enzyme having peroxide-resistant characteristics for use, by way of example, in a sensing device."

As described in the above-quoted section of the original patent application, one example of the predefined desired functionality can be the property of "peroxide-resistance."

For example, paragraph 23 of the original specification states:

"Embodiments of the invention are directed to processes for formulating a glucose oxidase enzyme with a particular desired property, such as, for example, an improved resistance to peroxide."

As described in the above-quoted section of the original patent application, an example of the predefined desired functionality is the desired property of "resistance to peroxide." However, a person of ordinary skill in the art would not be formulating enzymes without some predefined (preconceived) goal (desired function).

The Examiner states that Applicants citation to the specification at page 12, paragraph [0038] does not provide a specific definition for the phrase, but only gives one example of a "predefined, desired functionality." However, while Applicant's Appeal Brief dated August 15, 2007 includes remarks as discussed above, which are not addressed in the rejection raised in the Office Action of November 14, 2007. In particular, as noted above, claims 7-18 are definite and

clear (in compliance with 35 U.S.C. 112, second paragraph), in that the desired functionality would be understood as a desired property (such as, but not limited to, resistance to peroxide). The claimed method is one of formulating an enzyme, where claim 7 (and claims dependent thereon) includes "testing the colonies with active glucose oxidase for a predefined, desired functionality.

Given the clear description in the specification of testing for a desired functional property and the clear description of an example property, one skilled in the are would be able to understand that other tests of colonies with active glucose oxidase may be carried out for other desired functionality properties. As noted above, one skilled in the art would not be conducting tests without some goal (desired functionality) in mind. Thus, in concept and practice, the invention of claim 7 (and claims dependent thereon) would be understood and could be practiced (without undue experimentation) by one of ordinary skill in the art.

Furthermore, dependent claim 10 recites that testing the colonies for the predefined, desired functionality comprises placing an immobilized glucose oxidase in a sensor and testing the sensor. Thus, claim 10 further clarifies the testing portion of the method as involving testing a sensor. As described in paragraphs [0039] and [0046], the sensor may be introduced into an accelerated test environment to determine whether the particular enzyme is indeed functional or is suitable for use in a sensing device. One skilled in the art would understand that testing a sensor would involve testing the sensor for proper sensing functionality (ability to perform sensing functions in a desired environment of use). Consistent with the specification, new claim 19 is added herein (to depend from claim 10) that recites that testing the sensor comprises introducing the sensor into a test environment and testing the sensor for satisfactory sensing functionality.

In view of the foregoing, it is respectfully submitted that pending claims 7-10 and 11-18 (and new claim 19) are in compliance with 35 U.S.C. 112, second paragraph.

2. Response To Rejection Of Claims 1-3, 7-14 and 17 Under 35 U.S.C. 103(a):

Claims 1-3, 7-14 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al. This rejection is respectfully traversed in view of the following remarks.

Claim 1 recites a method for formulating an enzyme that is not disclosed by either Valdes et al., Cherry et al., or Hatzinikolaou et al., alone or in the combination proposed by the Examiner (which combination is respectfully traversed as discussed herein). For example, the method of claim 1 recites, among other features:

"obtaining an organism with a glucose oxidase gene; growing multiple colonies of the organism; altering the environment of the colonies; and screening the colonies to identify colonies with active glucose oxidase after altering the environment of the colonies."

Claim 1 recites several actions that, together, form the claimed method, where not any one or a combination of the above-cited references describes the combination of actions recited in claim 1. The cited references fail to teach, suggest or render predictable selecting pieces of the processes in Valdes et al., Cherry et al. and Hatzinikolaou et al. and combining them in the fashion that the Examiner suggests. Instead, the references, themselves, as well as other references of record teach a direction away from the present invention.

The mass of evidence of record in the application suggests that those skilled in the art were taking a direction that was completely different from that of the claimed invention. While the Examiner raises arguments as to obviousness to combine various parts of the cited references, none of the evidence of record supports the Examiner's proposal to select and combine portions of the various references. To the contrary, a number of references of record (including the primary reference relied upon by the Examiner) teach a direction different than the claimed invention and would lead one of ordinary skill in the art away from the claimed invention. Without the present disclosure as a guide, one of ordinary skill in the art would not have found it obvious to combine the above-cited references as suggested by the Examiner.

As described in more detail below:

a. The prior art of record does not teach or suggest or render predictable the claimed invention;

b. None of the prior art of record provide any teaching or suggestion or render predictable the combination of the Valdes et al, Cherry et al., and Hatzinikolaou et al., as proposed by the Examiner, and the mass of evidence of record shows that the prior art teaches away from the claimed invention; and

c. Each of dependent claims 2-3 and 7-8 recites further features that distinguish those claims from the prior art. Accordingly, those claims do not stand or fall with claim 1.

a. The Rejection Is Improper Because The Prior Art Does Not Teach Or Suggest Or Render Predictable The Claimed Invention.

In particular, neither Valdes et al. nor Cherry et al., nor Hatzinikolaou et al. describe formulating a glucose oxidase enzyme by growing multiple colonies of a organism, altering the environment of the colonies, and screening the colonies to identify colonies with active glucose oxidase after altering the environment of the colonies. Moreover, one of ordinary skill in the art would not have been led by the prior art of record to alter the environment of such colonies, much less screen for active glucose oxidase. Such procedures would have been a drastic departure from the state of the art and, without the benefit of the present specification as a guide, would not have been obvious to one of ordinary skill in the art.

The Examiner argues that Valdes et al. teaches that glucose oxidase in glucose sensors degrade over time due to hydrogen peroxide. The Examiner acknowledges that Valdes et al. do not teach a method of producing mutant glucose oxidase that is resistant to degradation from peroxide. (Office Action of November 14, 2008, pg. 5, ll. 12-14.) As discussed in more detail below, instead, Valdes et al. teach addressing peroxide degradation by adding a chemical catalase or by attaching an immobilized enzyme to a support that deactivates hydrogen peroxide. (Valdes, pg. 375, Left Column, ll. 6-18.

The Examiner refers to Valdes et al.'s statement than to ensure longer sensor functionality, instead of replacing a degraded glucose oxidase sensor enzyme with a fresh enzyme, it is advantageous to "prevent the degradation of the enzyme" (Office Action of November 14, 2007, pg. 5, ll. 3-6 and Final Office Action of January 16, 2007, pg. 4, l. 15 to pg. 5 l. 4., citing Valdes et al., pg. 375, ll. 2-5). The Examiner attempts to use that statement out of context, as a springboard to imply that Valdes et al. would have suggested a process involving altering the environment of the colonies of glucose oxidase organism and screening colonies in the manner recited in the present claims. However, Valdes et al. immediately follow the above statement with a description of the use of chemical additives as the so-called "better options." Accordingly, Valdes et al. teach a specific direction (use of chemical additives) that departs from the then-conventional process of replacing a degraded enzyme with a fresh enzyme.

Valdes et al. is not the only reference of record that teaches that the direction taken by those skilled in the art was to use chemical additives. Indeed, other references of record similarly teach that direction of the art (e.g., U.S. Patent No. 6,689,265 to Heller et al. and the article titled "Glucose ENFET doped with MnO_2 powder" by Yin et al.). Neither Valdes et al., nor any prior art of record that relates to peroxide degradation of glucose oxidase, describe or suggest altering the environment of the glucose oxidase colonies and screening the colonies for peroxide resistant properties for addressing peroxide degradation of glucose oxidase. Instead, as described in more detail below, Valdes et al. and other references of record show that the direction taken by those skilled in the art was away from the method of the presently claimed invention.

Because of this lack of disclosure in Valdes et al., the Examiner attempts to select pieces of each of the Cherry et al. and the Hatzinikolaou et al. references. However, neither of those references teach formulating a glucose oxidase enzyme by altering the environment of the glucose oxidase colonies to make them resistant to peroxide degradation.

For example, as noted above, claim 1 recites a method for formulating an enzyme that includes, among other features, "obtaining an organism with a glucose oxidase gene" and "growing multiple colonies of the organism." In addition, claim 1 recited "alterning the environment of the colonies" and "screening the colonies to identify colonies with active glucose oxidase after altering the environment of the colonies." The Examiner stated that Cherry et al.

disclose a method of making mutants of an enzyme which is also degraded in the presence of hydrogen peroxide, by using directed evolution techniques. (Office Action of November 14, 2007, pg. 5, ll. 18-21.) In addition, the Examiner stated:

"Cherry et al. discloses that after multiple rounds of directed evolution an enzyme, mutants of said enzyme that are resistant to deactivation in the presence of high concentration of hydrogen peroxide, conditions that mimic of hydrogen peroxide wherein the enzyme is normally deactivated, were obtained (pages 380-382). Cherry et al. discloses that colonies having enzymatic activity were selected to determine for its resistance against hydrogen peroxide (page 382)." (Office Action of September 20, 2007, pg. 6, ll. 9-17.)

However, Cherry et al., like Valdes et al., fail to disclose or suggest "obtaining an organism with glucose oxidase genes" and "growing multiple colonies of the organism." As such, Cherry et al. also fail to disclose or suggest "altering the environment" of such colonies or "screening" such colonies for active glucose oxidase after altering the environment of the colonies. Cherry et al. have nothing to do with glucose oxidase genes and would not teach or suggest growing colonies of an organism with glucose oxidase, or screening such colonies for active glucose oxidase. Instead, Cherry et al. describe production of a detergent additive (having no glucose oxidase) that is able to catalyze the oxidation of dyes that leach out of colored clothing during a wash cycle to render the dyes colorless and effectively prevent the transfer of dye to other clothes. (Cherry, et al., pg. 379, col. 1, ll. 24-29.)

According to Cherry, et al., "[i]n wash conditions using bleach-containing detergents, the elevated pH and high peroxide concentrations favor rapid formation of inactive form of the enzyme." Cherry et al. state that the "goal" of their work "was to develop a peroxidase variant effective as a dye-bleaching reagent in detergent." (Cherry et al., pg. 379, col. 2, ll. 7-11.) Cherry et al. teach to produce a dye-bleaching reagent in a clothes washing detergent and do not teach or suggest anything to do with obtaining an organism with a glucose oxidase gene and growing multiple colonies of the organism, much less screening such colonies for active glucose oxidase after altering the environment of the colonies

The Examiner's apparent attempt to rely on Cherry et al. as teaching of directed evolution of enzymes, in general, to be resistant to peroxide takes Cherry et al.'s disclosure far out of context. **The only reason that Cherry et al. is concerned about peroxide resistance is because Cherry et al.'s stated goal was to develop a dye-bleaching reagent in a clothes washing detergent (where "wash conditions" have "high peroxide concentrations").** Cherry et al.'s "inactivation conditions were designed to mimic those found in washing machines using bleach containing commercial detergents," at pH levels and temperatures ("40-50 C") inconsistent with the production of glucose oxidase. (Cherry et al., pg. 380, col. 1, ll. 19-21.) There is no logical relation between Cherry et al.'s clothes washing detergent (or the high peroxide environment of a clothes wash cycle) and glucose oxidase enzymes for glucose sensors. Cherry et al.'s reference to peroxide resistance and inactivation conditions for a dye bleaching reagent in a wash cycle would not teach or suggest anything to one skilled in the art about glucose oxidase, much less to obtain an organism with a glucose oxidase gene, grow multiple colonies of the organism and/or screen such colonies for active glucose oxidase after altering the environment of the colonies.

The context in which Cherry et al. refer to peroxide resistance (clothes washing environments) would not have been ignored by one of ordinary skill in the art. Such contexts (and environments) are inconsistent with the production of glucose oxidase. Thus, like Valdes et al., Cherry et al. fail to disclose or suggest the invention recited in claim 1.

The Examiner stated that Hatzinikolaou et al. discloses a library of glucose oxidase genes known in the art. (Office Action of November 14, 2007, pg. 6, ll. 5-6.) However, Hatzinikolaou et al. describe isolating and characterizing a new synthesized glucose oxidase for purposes of conducting certain specified analyses (described on pages 373 and 374 of the Hatzinikolaou et al. reference), none of which relate to resistance to hydrogen peroxide (claim 3), or altering the environment of the glucose oxidase organism colonies and thereafter screening the colonies for active glucose oxidase (claim 1).

While gene libraries have been employed by those skilled in the art for gene analysis, Hatzinikolaou et al. provide no suggestion to use such libraries in the formulation of an enzyme by directed evolution. Hatzinikolaou et al. teaching of using gene libraries to analyze

characteristics of a gene provides no motivation or suggestion or render predictable to do anything more than to analyze the specific new synthesized glucose oxidase for the specific characteristics described on pages 373 and 374 of that reference. The Examiner has picked only the feature of forming a gene library of glucose oxidase gene from Hatzinikolaou et al.'s overall process and seeks to combine that teaching with Valdes et al. and Cherry et al.

However, Hatzinikolaou et al.'s purpose of forming a library of a new simulated glucose oxidase (for analyzing the characteristics of the new simulated glucose oxidase described in that reference) would have no applicable purpose in any mutation process described by Cherry et al. Once Hatzinikolaou et al. obtains and isolates a sample of the new glucose oxidase, Hatzinikolaou et al. conducts analysis on the isolated sample. Mutating the sample would not allow Hatzinikolaou et al. to analyze the characteristics of the simulated glucose oxidase (as the mutations could effect the detection of characteristics under analysis). Accordingly, it would not have been obvious to look to Hatzinikolaou et al. as a teaching of growing multiple colonies of an organism with a glucose oxidase, altering the environment to the colonies and screening the colonies to identify colonies with peroxide resistant properties. The Examiner's suggestion to combine Hatzinikolaou et al. with Cherry et al. is, therefore, respectfully traversed. Moreover, Hatzinikolaou et al. does not disclose or suggest screening colonies for active glucose oxidase after altering the environment of the colonies.

Because Cherry et al. do not relate to growing multiple colonies of an organism with a glucose oxidase gene or altering the environment of such colonies, it follows that Cherry et al. also do not describe screening such colonies by determining whether the colonies contain active glucose oxidase. Also, Hatzinikolaou et al. provide no teaching or suggestion of growing such colonies with a glucose oxidase gene and screening such colonies for active glucose oxidase after altering the environment of such colonies. While the combination of those references is traversed for reasons noted above, no combination of those references could lead to growing such colonies and screening the colonies for active glucose oxidase, because neither of those references, describe such features. Moreover, as noted above, Valdes et al. also do not teach screening colonies for active glucose oxidase after altering the environment of the colonies and, instead, teach a very different direction (addition of chemicals to reduce peroxide degradation).

Accordingly, the Examiner's suggestion to combine Valdes et al. with Cherry et al. and Hatzinikolaou et al. is traversed and would not lead to the present invention.

None of the cited references describes or suggests creating colonies of an organism with a glucose oxidase gene, altering the environment of the colonies and then screening colonies for active glucose oxidase. Accordingly, the combination of the references (as suggested by the Examiner) could not result in the claimed invention. The rejection of claims 1-3, 7-14 and 17 under 35 U.S.C. 103(a) is, therefore, respectfully traversed and should be reversed.

b. The Rejection Is Improper Because Prior Art Provides No Motivation To Combine And Teaches Away From The Combination Suggested By The Examiner.

Because of the above-noted lack of disclosure in Valdes et al. (of growing multiple colonies of the glucose oxidase organism and screening the colonies to identify colonies with active glucose oxidase after altering the environment of the colonies), the Examiner attempts to select pieces of each of the Cherry et al. and Hatzinikolaou et al. references, and combine those with the Valdes et al. reference.

None of the Valdes et al, Cherry et al. nor Hatzinikolaou et al. references provide any teaching of creating multiple colonies of glucose oxidase containing organism, altering the environment of the colonies and screening colonies for active glucose oxidase. Rather, Valdes et al. teach away from such methods by, instead, referring to **conventional procedures that use additives for deactivating or destroying hydrogen peroxide** and, thus, teach away from such a method, as follows:

"To prohibit the H_2O_2 from degrading the GOD enzyme, it has been proposed that catalase be coimmobilized with GOD... The addition of catalase in either the GOD itself, or to the incubating solution has resulted in a slower deactivation of the GOD enzyme ... A long term remedy of the degradation of GOD by H_2O_2 could be the immobilization and attachment of the enzyme to a support that deactivates H_2O_2, as it is being produced. Such as study was conducted by Cho[2], using the peroxide decomposition catalyst, activated carbon. In a study conducted by Carter[19], the best results were obtained with activated carbon, impregnated with ruthenium. This

combination was able to destroy hydrogen peroxide and stabilized the enzyme." (Valdes et al., pg. 375, col. 1, l.18 to col. 2, l. 6.)

Not only does Valdes et al. fail to teach or suggest to alter the environment of glucose oxidase colonies or to screen the colonies to identify colonies with active glucose oxidase, but, in the above-quoted statement, Valdes et al. further teaches to use other, very different procedures (conventional in the art) to address degradation effects of peroxide on glucose oxidase. Thus, the Valdes et al. reference shows that the direction taken by those most skilled in the art involved employing materials, additives, or the like that deactivate peroxide.

Additional art of record also describes conventional "additive" processes for removing or neutralizing peroxide such as by adding an antioxidant or peroxidase to the glucose oxidase to break down peroxide or by coating the glucose oxidase enzyme with a protective coating, including U.S. Patent No. 6,689,265 to Heller et al. and the article titled "Glucose ENFET doped with MnO_2 powder" by Yin et al. Those references further emphasize that, prior to the present invention, the direction taken by those skilled in the art for addressing the peroxide degradation of glucose oxidase was wholly different from the direction of the present invention. In U.S. Patent No. 6,689,265 to Heller et al., a peroxide generating enzyme may include a sufficiently thick, natural, electrically insulating protein or glycoprotein layer. (See column 6, lines 59-67 of the Heller et al. patent) Heller et al. also disclose an alternative embodiment in which a peroxide generating enzyme is immobilized in a non-conducting inorganic or organic polymeric matrix. (See column 7, lines 3-11 of the Heller et al. patent) Also, Heller et al. describe a first layer enzyme 11 (peroxidase) that reduces peroxide generated from a second layer (glucose oxidase layer) 13. The Yin et al. article describes the addition of MnO_2 to catalyze peroxide and produce water and oxygen therefrom. (Yin, Exhibit 2, Abstract and pg. 188, col. 1, ll. 20-34.)

Thus, both the Heller et al. patent and the Yin et al. article show that the direction taken by those skilled in the art is to provide additives or complex multi-layer sensor structures to remove hydrogen peroxide. These references, in addition to Valdes et al.'s express references to conventional uses of additives, show that those skilled in the art were not considering growing, altering and screening colonies for peroxide resistance glucose oxidase organism, but instead were attempting to address the peroxide production issue by removing or neutralizing peroxide

with additives (not by altering the glucose oxidase). The state and direction of the industry, as evidenced by Valdes et al., Heller et al. and Yin et al., was a wholly different direction than that taken by the present Applicants (including altering the environment of the glucose oxidase colonies, screen the colonies to identify colonies with active glucose oxidase after altering the environment of the colonies (claim 1). Accordingly, the mass of evidence of record (including the primary reference relied upon by the Examiner) teaches one skilled in the art taking a direction different from (and away from) the present invention.

The mass of evidence of record showing the direction of the industry (away from that of the present invention) cannot be ignored. Without the present disclosure as a guide, one of ordinary skill in the art would not have found Valdes et al.'s discussion of the degradation of glucose oxidase as a prompt or suggestion to employ a mutation process for detergent as described Cherry et al. Instead, as noted above, one of ordinary skill in the art would have looked to conventional manners of removing peroxide, such as additives for removing or neutralizing peroxide. Accordingly, the rejection of 1-3 and 7-8 under 35 U.S.C. 103(a) is further respectfully traversed.

The fact that the primary reference (Valdes et al.) teach away from the clamed invention and the combination suggested by the Examiner, shows that a *prima facie* case of obviousness has not been raised. Numerous Federal Circuit decisions recognize that an invention will not be deemed obvious in a patent law sense when one or more prior art references "teach away" from the invention. For example, the Federal Circuit stated "as a useful general rule, that references that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354, 60 USPQ2d 1001 (Fed. Cir. 2001). Last April, *KSR Int'l Co. v. Teleflex Inc*, the U.S. Supreme Court again acknowledged that principle, by citing its previous decision in *Untied States v. Adams*, 383, U.S. 39, 40 (1966), in which the Court relied upon a principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. The U.S. Supreme Court further stated "[a]s is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was,

independently known in the prior art." (*KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).)

Furthermore, "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003). Also see, *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990) (the closest prior art reference "would likely discourage the art worker from attempting the substitution suggested by [the inventor/patentee]") and *Singh v. Brake*, 317 F.3d 1334, 1346, 65 USPQ2d 1641 (Fed. Cir. 2003)("whether or not a reference 'teaches away' from a claimed invention" is "relevant in determining whether or not a claimed invention would have been obvious").

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. (underline added for emphasis.) *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351—52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the *Graham* factors).

Conclusory statements that prior art references provide motivation to combine, or statements of motivation derived from the Applicant's own specification, are not sufficient to set forth a *prima facie* case of obviousness. "The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124— 25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard. Inc., v. M3* Systems, *Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there

must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine,* 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined *only* if there is some suggestion or incentive to do so.') (emphasis in original) (quoting *ACS Hosp.* Sys., *Inc. 'v. Montefiore Hosp.,* 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

As noted above, the Examiner has not shown any motivation or suggestion in the prior art that would have led one skilled in the art to grow colonies of an organism with a glucose oxidase gene, alter the environment of those colonies and screen for active glucose oxidase after altering the environment. In fact, Valdes et al and other prior art of record show that altering the environment and screening process for glucose oxidase would have been a drastic diversion from the direction taken by those most skilled in the prior art when seeking to address peroxide degradation of glucose oxidase.

The legal authority expresses the requirement for a showing of specificity in the prior art of motivation to select components to combine. *See, e.g., In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); *In re Rouffet,* 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); *In re Fritch,* 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references").

While the Valdes et al., Cherry et al. and Hatzinikolaou et al. references, themselves, provide no motivation or suggestion, the Examiner argues that one of ordinary skill in the art would have been motivated to do so to formulate or produce mutant glucose oxidase that is

resistant to peroxide (Office Action of November 14, 2007, pg. 6, ll. 10-13). While this is the likely conclusion, after reading the present disclosure as a guide, the references of record actually teach to do something very different (add chemicals) to reduce peroxide degradation of glucose oxidase. Thus, the mass of evidence of record shows that the motivation provided by the cited references would have been to reduce peroxide degradation by adding chemicals as taught by Valdes et al., U.S. Patent No. 6,689,265 to Heller et al. and the article by Yin et al.

The Examiner further argues that "[o]ne of ordinary skill in the art would have been motivated to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide." (Office Action of November 14, 2007, pg. 6, ll. 19-22.) However, as noted above, one of ordinary skill in the art would not have ignored Valdes et al.'s (and others) express teaching of using additives to address peroxide degradation and, thus, would have been taught in a direction away from producing mutations of glucose oxidase to address peroxide resistance. The record shows that the cited references (and Valdes et al., in particular) would have motivated those skilled in the art in a direction away from the present claims.

In addition, the Examiner argues that one of ordinary skill in the art would have had a "reasonable expectation of success." However, without the present disclosure as a guide, one of ordinary skill in the art would not have selected altering the environment of glucose oxidase organism colonies, screening the colonies, purifying, isolating and measuring processes to modify Valdes et al.'s disclosed solution to peroxide degradation of glucose oxidase. Valdes et al. teaches solutions to the peroxide degradation problem (by using chemical additives) and would have led one skilled in the art in the direction of those solutions.

Cherry et al. do not mention glucose oxidase anywhere in their disclosure. Moreover, the only relevance that Cherry et al. has to peroxide is in the context of a clothes washing detergent and a clothes washing environment (pH and temperature) that would not be compatible with the production of glucose oxidase for biological sensors. Thus, Cherry et al. does not address the deficiency of Valdes et al.

Hatzinikolaou et al. fails to provide any motivation or suggest any relation to altering the environment of the glucose oxidase organism colonies or of addressing peroxide degradation of glucose oxidase. Moreover, the whole purpose of Hatzinikolaou et al. (to analyze a specific new simulated glucose oxidase) is not consistent with Cherry et al.'s mutation process.

The Examiner's conclusory statements of suggestion to combine, and the Examiner's argument of "reasonable expectation of success," fail to address the significant issue of why one skilled in the art would have been motivated to select a process as described by Cherry et al., to change the direction taken by those most skilled in the prior art as described by Valdes et al. The Examiner's argument that a "reasonable expectation of success" would have motivated the combination, is contrary to the express teachings of the prior art. The prior art teaches that those most skilled in the art were taking a wholly different direction to address peroxide degradation of glucose oxidase and, thus, would have found it unreasonable (not reasonable) to change the course of direction from that of the state of the art.

More specifically, Valdes et al. refer to completely different directions taken by those most skilled in the art, whereby the glucose oxidase enzyme is immobilized and attached to a support that deactivates peroxide. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference,... would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999). Valdes et al., directly refers the reader to conventional methods of addressing peroxide degradation of glucose oxidase that employ additives for destroying or neutralizing peroxide (which is quite different from creating multiple colonies, altering the environment and screening for desired peroxide resistant properties).

Because the Examiner has not shown any motivation or suggestion in the prior art that would have led one skilled in the art to select Cherry et al.'s mutation process and materially change the direction taught by the Valdes et al. reference, the Examiner has not raised a *prima facie* case of obviousness. Therefore, the rejection of 1-3, 7 and 8 under 35 U.S.C. 103(a) is respectfully traversed.

c. Each of dependent claims 2, 3, 7-14 and 17 recite further features that distinguish those claims from the prior art.

Each of dependent claims 2, 3, 7-14 and 17 recite further featured that distinguish those claims from the prior art. In particular, each of those claims recites features relating to altering the environment of the colonies and screening the colonies to identify colonies with active glucose oxidase. As described above, neither the Valdes et al., Cherry et al., nor Hatzinikolaou et al. references describe or suggest or render predictable altering the environment of the colonies and screening the colonies for active glucose oxidase after altering the environment. In that regard those references also do no disclose or suggest the additional processing recited in dependent claims 2, 3, 7-14 and 17, including:

1. "the organism is selected from a group consisting of *Aspergillus Niger, Penecillium funiculosum, Saccharomyes cervisiae, and Escherichia Coli*" (claim 2);

2. "altering the environment of the colonies comprises introducing peroxide to the colonies" (claim 3);

3. "testing the colonies with active glucose oxidase for a predefined, desired functionality after screening the colonies to identify colonies with active glucose oxidase" (claim 7); and

4. "continuing to alter the environments of the colonies until the colonies with active glucose oxidase are of a suitable number to proceed with testing the colonies with active glucose oxidase for the predefined, desired functionality" (claim 8).

5. "testing the colonies with active glucose oxidase for the predefined, desired functionality comprises employing glucose oxidase from the colonies in sensors" (claim 9);

6. "testing the colonies further comprises: extracting glucose oxidase from the colonies; immobilizing the glucose oxidase after extracting the glucose oxidase from the colonies; placing the immobilized glucose oxidase in a sensor; and testing the sensor" (claim 10);

7. "extracting glucose oxidase from the colonies comprises employing an ionic column to extract glucose oxidase from the colonies" (claim 11);

8. "extracting glucose oxidase from the colonies comprises: removing the glucose oxidase from the colonies; purifying the glucose oxidase; and characterizing the glucose oxidase" (claim 12);

9. "removing the glucose oxidase from the colonies comprises grinding the colonies in a homogenizer into cell components" (claim 13);

10. "removing the glucose oxidase from the colonies further comprises fractionating the cell components employing centrifugation and differential solubility after grinding the colonies in a homogenizer" (claim 14);

11. "purifying the glucose oxidase comprises purifying the glucose oxidase by employing chromatography methods" (claim 17).

The rejection of claims 2, 3, 7-14 and 17 is, therefore respectfully traversed and should be withdrawn.

3. Response To Rejection Of Claims 15 and 16 Under 35 U.S.C. 103(a)

Claims 15 and 16 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Valdes et al., Cherry et al., and Hatzinikolau et al. as applied to claims 1-3, 7-14 and 17 above, and further in view of MISONIX.

This rejection is respectfully traversed at least for reason discussed above with respect to claim 1. Each of claims 15 and 16 is indirectly dependent on claim 1. Accordingly, the distinctions noted above between claim 1 and the cited Valdes et al., Cherry et al. and Hatzinikolaou et al. references apply to claims 15 and 16, as well. The MISONIX reference was not relied upon by the Examiner to address those distinctions. Instead, the Examiner cited the MISONIX reference as allegedly teaching of disrupting cells via sonication.

Accordingly, at least for reasons discussed above with respect to claim 1, the rejection of claims 15 and 16 is respectfully traversed.

Furthermore, while the Examiner stated that "[o]ne of ordinary skill in the art would have been motivated to [combine the teachings of Valdes et al., Charry et al. and Hatzinikolaou et al. with MISONIX] in order to disrupt cells comprising mutant glucose oxidase" and "would have had a reasonable expectation of success since disruption of cells using sonication is well known and practiced routinely in the art.". However, MISONX does not provide any motivation or suggestion of disrupting glucose oxidase cells in a process as recited in claims 15 and 16, where glucose oxidase is extracted from colonies that have been screened for active glucose oxidase by disrupting cell components via sonication (claim 15) and fractionating the cell components employing centrifugation and differential solubility after disrupting the colonies via sonication (claim 16).

The Examiner's comments do not address the features of fractionating the cell components employing centrifugation and differential solubility after disrupting the colonies with sonication. Accordingly, the Examiner has failed to provide a prima facie case of obviousness of claim 15 or of claim 16. The rejection of claim 15 and 16 is traversed and should be withdrawn.

4. Response To Rejection Of Claims 4, 5 and 6 Under 35 U.S.C. 103(a)

Claims 4-6 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Valdes et al., Cherry et al., and Hatzinikolau et al. as applied to claims 1-3, 7-14 and 17 above, and further in view of Wagner and Aldrich Catalog.

This rejection is respectfully traversed at least for reason discussed above with respect to claim 1. Each of claims 4-6 is directly or indirectly dependent on claim 1. Accordingly, the distinctions noted above between claim 1 and the cited Valdes et al., Cherry et al. and Hatzinikolaou et al. references apply to claims 4-6, as well. The Wagner reference was not relied upon by the Examiner to address those distinctions and does not address the above-noted distinctions between the claims and the Valdes et al., Cherry et al. and Hatzinikolaou references.

Indeed, the Wagner reference was cited, according to the Examiner, for disclosing a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission

from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission. However, Wagner does not teach or suggest formulating a glucose oxidase enzyme by growing colonies, altering the environment of the colonies and screening the colonies for active glucose oxidase after altering the environment. Accordingly, the combination of Wagner with the above-discussed references (the Valdes et al., Cherry et al. and Hatzinikolaou references) would not lead to the presently claimed invention.

The Examiner also cited the Aldrich Catalog as describing Leuco-crystal violet dyes as common fluorescent dyes. The cited portion of the Aldrich Catalog neither describes nor suggests formulating an enzyme, much less growing colonies, altering the environment of the colonies and screening the colonies for active glucose oxidase after altering the environment.. Accordingly, the cited portion of the Aldrich Catalog does not address the above-noted distinctions between the claimed invention and the Valdes et al., Cherry et al., Hatzinikolaou et al. and Wagner references. Thus, the combination of the cited portion of the Aldrich Catalog with those other references (as suggested by the Examiner) could not result in the claimed invention.

Accordingly, the rejection of claims 4-6 is respectfully traversed.

5. Conclusion:

In view of the foregoing, it is respectfully submitted that claims 1-17 are in condition for allowance and the application should be allowed in its present form.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: 4/9/08

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